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Management and outcome after local recurrence of osteosarcoma

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Abstract

We report on the management and outcome of 96 patients who developed local recurrence (LR) after having definitive primary treatment with chemotherapy and surgery for non-metastatic osteosarcoma. LR developed at a median of 11 months from initial surgical treatment. 18% of patients had metastases prior to the diagnosis of LR and 23% were found to have metastases synchronously. The prognosis for this group with metastases was 14% survival at 2 years. In the 57 patients without metastases at the time of development of LR, survival was 51% at 2 years and 41% at 5 years. Treatment was by excision of the LR and radiotherapy or by amputation. The only significant prognostic factors identified were the presence of metastases at the time of development of LR ($P < 0.0001$) and small size of the LR. The role of adjuvant chemotherapy was unclear. Whilst every attempt should be made to avoid LR, patients who develop LR are curable, particularly if they do not have metastases at the time of diagnosis of the LR.

Keywords: Osteosarcoma; Local recurrence; Survival; Prognostic factors

1. Introduction

Survival rates for osteosarcoma have improved dramatically in the past 20 years due to improvements in the effectiveness of chemotherapy [1,2]. However, adequate surgical excision remains an essential part of the treatment of osteosarcoma [3]. An inability to completely resect the tumour results in a high risk of local recurrence (LR) and a worse prognosis.

It was anticipated that the increasing use of limb salvage surgery (LSS) would significantly increase the risk of LR over and above that found with amputation and there was initially some speculation that this may adversely effect survival [4]. This has never been shown to be the case and more recent publications have shown mixed results in determining the significance of LR on the overall survival of patients with osteosarcoma [5].

However, there is general agreement on the risk factors that lead to LR. Three factors have been reported to consistently lead to an increased risk of LR – inadequate margins of excision (intralesional or marginal excision), limb salvage surgery as opposed to amputation and a poor response to pre-operative chemotherapy [6,7]. Other factors including the size of tumour, site and age have also been implicated [7,8].

Whilst the factors that lead to LR have been well documented, the outcome for patients with LR has not been well established. Several authors have suggested that patients with LR have a worse outlook than those with metastatic disease, whilst others suggest that it is invariably fatal [9,10].

In order to establish the significance of LR in the course of the disease process for patients with osteosarcoma, we have reviewed the management and outcome for all patients with LR in osteosarcoma treated at our centre.

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2. Patients and methods

We have followed up all patients treated surgically for osteosarcoma in the past 25 years, allowing a minimum period of follow-up of 2 years. Between 1976 and 2001, we have treated 886 patients with high-grade primary non-metastatic osteosarcoma according to well-defined protocols either entering patients into chemotherapy trials run by the Medical Research Council (MRC)/European Osteosarcoma Intergroup (EOI) or using cisplatin and doxorubicin [11,12]. All patients have undergone resection of their tumour with the intention of achieving wide surgical margins whenever possible [13]. During this time period, 85% of patients with osteosarcoma had LSS and 15% had an amputation. 96 patients developed a local recurrence at some stage following their initial treatment, and these were confirmed by imaging and histology. The management and outcome for this group of patients forms the group under study in this report.

We have investigated the following factors in assessing the outcome of patients with LR in osteosarcoma: Time to LR from initial surgery; effectiveness of initial chemotherapy (% necrosis), size of initial tumour, site of LR (bone or soft tissue), size of LR (cms); surgical management of LR (excision or amputation); use of further chemotherapy (yes (Y)/no (N)); use of radiotherapy; time to development of metastases (prior to LR, synchronous with LR, following LR) and overall survival time.

Overall survival from time of local recurrence was calculated using Kaplan–Meier survival curves and the impact of prognostic factors was assessed using the log-rank test [14,15]. Multivariate analysis was performed using Cox's proportional hazard method with variables being chosen using a forward conditional stepwise approach. Relative Risks have been calculated using a proportional hazards model with only the noted covariate in the model. Significance was set at $P < 0.05$ for two-sided tests. Survival time was calculated from the time of local recurrence when investigating the significance of tumour and patient characteristics. The end-point was taken as the time of death or the last documented time the patient was known to be alive. Analyses were performed using Statview [16]. When factor analysis was undertaken, the numbers involved have been highlighted.

3. Results

Of the 96 patients who developed LR, 90 had originally undergone limb salvage surgery and 6 had undergone amputation. The median age of these patients was 16 years (range 5–71 years), the same as the total population with osteosarcoma, and the male/female ratio was 56:40. The site of LR was the distal femur in 43 patients, followed by the proximal humerus in 12 patients. 14 patients had had a previous pathological fracture. In only 11% of the patients had there been a good response (>90% necrosis) to chemotherapy, whilst in the remainder there had been a poor response. 38% of the patients had been documented to have clear margins at the time of initial surgical excision (wide or radical), whilst the other 62% had close or involved margins (48% marginal and 14% intralesional). Only one patient developed LR after having a wide excision and a good response (>90% necrosis) to chemotherapy whilst 44% of those who developed LR had both a poor response to chemotherapy and a close or involved margin of excision. Five of these patients had received postoperative radiotherapy to try and decrease the risk of LR developing.

The median size of the primary tumours was 10 cm (range 3–22 cm) and the median size of the local recurrence was 3.5 cm (range 2–20 cm).

The median time to develop LR was 13 months from the date of diagnosis and 11 months from the date of surgery, with a range from 1 to 66 months (Fig. 1). The risk of developing LR decreased with time and 60% of LRs arose within 12 months of initial surgery and 82% within 24 months. The time to development of LR was not significantly different for those patients who had a good/bad response to chemotherapy, those who did/did not have metastases, those who had limb salvage or amputation or by the adequacy of the initial margin. The one patient who developed LR after five years had undergone numerous operations for lengthening of an extendible prosthesis which subsequently became infected. She developed a spontaneous haematoma around her prosthesis just a few months after a successful two-stage revision to eradicate the

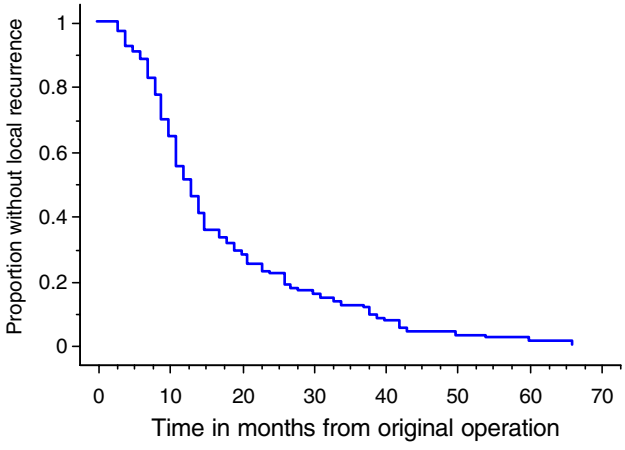

Fig. 1. Graphical representation showing time taken before patients developed local recurrence (LR) following primary surgical treatment for osteosarcoma in all 96 patients.

infection. It was subsequently found to be a LR and she had a high above knee amputation.

At the time of development of LR, 17 patients (18%) were already known to have metastases, 22 patients (23%) were found to have them synchronously at the time of restaging (within 6 weeks of the identification of LR) and 37 (38%) were found to have them later. At a minimum follow-up of 2 years since LR, 20 patients (21%) have not yet developed metastases. For the purposes of further evaluation, those patients who did NOT have metastases identified at the time of development of their LR or shortly afterwards will be considered to have 'localised' recurrence ($n = 57$), whilst those who had metastases synchronously or previously will be considered to be 'metastatic' ($n = 39$).

The risk of developing metastases was related to the original effectiveness of the chemotherapy used. In those with a good response (>90% necrosis), only half developed metastases compared with 78% of those with a poor response.

Of the 96 patients with LR, 20% arose in bone and 80% in soft tissue. For the 30 patients where data on the mode of presentation was available, 14 of the LRs were detected by the patient noticing a lump, 10 at the time of routine follow-up and 6 by routine radiographic imaging when LR was not expected clinically. The size of LR detected by the patients and by the radiographs averaged 4.5 cm, but that detected by routine clinical examination was 9 cm, although this difference was not found to be significant ($P = 0.12$).

The management of the LR was different depending upon the perceived disease status of the individual and is summarised in Table 1.The management varied depending upon the location and size of the LR. 72 patients had the LR surgically excised with only two of the 57 patients with localised disease not having this (both refused amputation and entered a chemotherapy trial, but developed metastases and received palliative radiotherapy). 36 of the 57 patients with localised disease had an amputation with the other 19 having a local excision, 13 of them having subsequent radiotherapy. Of the 39 patients with metastatic disease, 9 had excision of their LR, but 8 required an amputation. The median size of LR in patients undergoing amputation was 8 cm, whilst in those undergoing local excision, it was 3 cm. Amputation was needed far more often for bony recurrences, whilst local excision was usually feasible for soft tissue recurrences. Macroscopically clear margins were achieved in all cases.

Table 1
Treatment of patients depending on disease status at the time of diagnosis of local recurrence (LR)

	Patients with known metastatic disease ($n = 39$)	Patients with 'localised' disease ($n = 57$)
Palliation only	7	0
Excision only	5	27
Excision + chemotherapy	3	15
Excision + radiotherapy	4	10
Excision + radiotherapy + chemotherapy	5	3
Chemotherapy alone	5	0
Radiotherapy alone	8	0
Chemotherapy + radiotherapy	2	2

Complete local control was achieved in 67 of the 72 patients (93%) who had surgical removal of the LR. Further LR arose in 5 patients, 4 of whom had undergone a local excision and radiotherapy and in one who had an amputation. Three of these patients were in the metastatic group and two in the 'localised' group. Further LR was associated with the development of metastases and all five patients subsequently died. Because of the low numbers and numerous treatment methods, it was impossible to identify any factor leading to better local control.

Of the 17 patients who had metastases prior to the development of LR and for the 22 who were found to have metastases synchronously with LR, the median survival from time of LR was 5 months and 7 months, respectively. The one year survival was 30% and the two year survival was 14%. (Fig. 2). Only two patients have survived beyond three years and both have undergone repeated metastasectomies for recurrent lung metastases following removal of their LR. The survival in patients without metastases at the time of LR was 68% at one year, 51% at two years, 41% at 5 years and 36% at 10 years. This was a highly significant difference compared with those patients with metastases (Hazard Ratio (HR) 3.98 for those with metastases, CI 2.36–6.71, $P < 0.0001$).

57 patients did not have any evidence of metastases at the time of development of LR and thus were considered

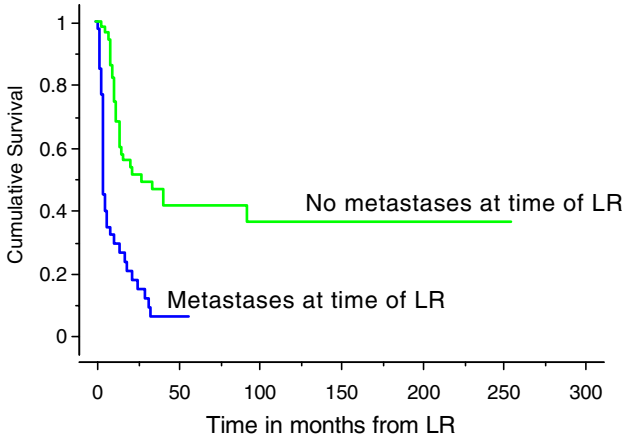

Fig. 2. Kaplan–Meier survival curve showing the likelihood of survival from time of local recurrence in patients who did/did not have metastases at the time of diagnosis of their local recurrence ($P < 0.0001$).

potentially curable. 37 subsequently developed metastases at a median time of 7 months (range 2–67 months) from the development of LR (Fig. 3). 20 have not developed metastases at a median follow-up time of 25 months (range 1–255 months). The risk of developing metastases is shown in Fig. 4. One patient developed LR at 15 months following a proximal femoral replacement, was treated by hindquarter amputation and developed a solitary metastasis 67 months later. This was resected and he died of unrelated causes four years later. Of those who developed metastases, 30 have died at a mean time of 17 months from development of LR compared with two in those 20 patients who did not develop metastases. One of these patients died at 5 months from LR due to a cardiomyopathy whilst a second died 170 months after the diagnosis and treatment of the LR from leukaemia. The survivorship of patients who were thus potentially 'curable' at the time of development of LR, was 51% at 2 years and 41% at 5 years.

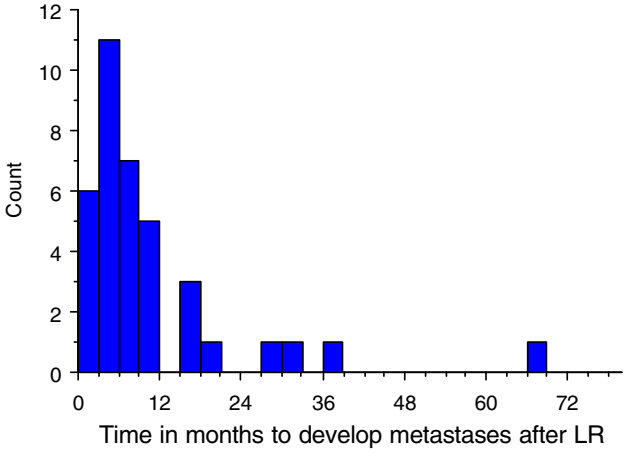

Fig. 3. Graph to show number of patients subsequently developing metastases following the diagnosis and treatment of their LR when they did not have metastases at the time of LR ($n = 57$).

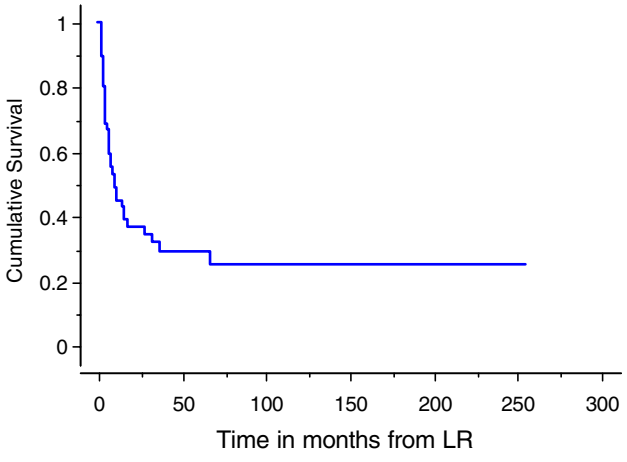

Fig. 4. Kaplan–Meier curve showing proportion remaining free of further disease in those patients found not to have metastases at the time of presentation of their LR ($n = 57$).

Table 2
Risk factors for survival

Factor	*P* value	Hazard ratio + C.I.
Metastases at diagnosis of LR	<0.0001	3.98 (2.36–6.71)
LR arising after 2 years	0.507	0.81 (0.43–1.52)
LR arising after 1 year	0.105	0.66 (0.40–1.09)
LR size > 5 cm	0.0089	10.588 (1.8–61.7)
Initial chemotherapy response <90% necrosis	0.356	1.62 (0.58–4.56)
Surgical excision of LR	<0.0001	6.36 (3.58–11.29)
Second-line chemotherapy	0.407	1.237 (0.748–2.046)

In those patients without metastases at the time of development of LR and who were thus thought to be potentially curable, the only prognostic factor identified was whether or not the patients subsequently developed metastases ($P < 0.0001$). There was a trend for patients who developed LR more than twelve or 24 months after the initial operation to do better, whilst a small size of LR (<5 cm) was significant for a better overall survival (Table 2). The original percentage necrosis following chemotherapy, the size of the original tumour and the original margin of excision were non-significant. Patients who had their LR treated by amputation tended to do worse, probably because they had larger LRs ($P = 0.051$), but surgical excision was mandatory for survival. There was no significant difference in outcome in patients having local control measures alone (surgery ± radiotherapy) with those who did or did not have systemic therapy (chemotherapy).

Second-line chemotherapy was used in 36 of the 96 patients. The choice of drugs varied considerably as these patients were treated at a variety of oncology centres where both the decision as to the use, or otherwise, of chemotherapy and what agents to use was left to the treating clinician. More recently, regimes used either ifosfamide or high-dose methotrexate. Due to the low numbers and variety of regimes used, no useful information could be obtained about outcome with different chemotherapy usage. Even in the 57 patients with 'curable' disease, the survival curves for patients who had or did not have chemotherapy were identical.

4. Discussion

This paper has sought to investigate the outcome for patients who develop LR following initial treatment for osteosarcoma. We have not investigated risk factors for the development of LR as these are well established, nor have we investigated the significance of LR as a prognostic factor for survival in patients with LR [17–19].

We have identified 96 patients who developed LR over a 25-year period. During this time, an average of 85% of patients will have had LSS compared with 15% having amputation. Furthermore, most patients will have received chemotherapy using one of the regimes advocated by the EOI and reported in their various papers [11,12]. The chemotherapy regimes used have only produced a good response (>90% necrosis) in 28% of patients, a considerably lower figure than has been reported in other national studies over a similar time period [20,21]. Thus, the combination of high limb salvage rates and relatively ineffective chemotherapy may explain the relatively high LR rate we experienced of 11%. However, this paper is not about the causes of LR, but is about it's management.

The diagnosis of LR was not always easy to make and the mean size of the LRs at the time of detection was 5.6 cm. We have not routinely followed up patients with regular magnetic resonance imaging (MRI) to specifically detect LR, relying on routine clinical and plain radiographic assessment. Whilst some protocols recommend regular MRI or bone scans for detection of LR at an early stage, this has never been shown to be cost-effective. In the earlier years of this study, MRI was not available and there was a trend for the LRs to be detected later and thus when they were larger. Given the significantly increased risk of LR in patients with a poor response to chemotherapy and close margins of excision, there would certainly seem to be a rationale for directing any future protocols for detection of LR specifically at this group. There may be a place for the routine use of Ultrasound, MRI or positron emission tomography (PET) scanning in this group and a specific study investigating this may be justified. Unfortunately, for many patients, the documentation about how the LR was detected was not available. We found that almost half of the LR were detected by patients themselves noting a new lump, whilst the other half were detected by routine investigation. A patient education programme about how to detect LR may thus be beneficial and could supplement other follow-up investigations.

What can be stated with some certainty is that any patient with LR is at a very significant risk of developing metastatic disease. In this series, 17 patients already had metastases at the time of diagnosis of LR and of the remaining 79, 59 (75%) were either found to have metastases synchronously or developed them later. Clearly, very careful staging of any patient with a LR is mandatory and subsequent regular review is essential.

Whether LR is itself a poor prognostic factor is as yet unresolved. Ferrari and colleagues [22,23] reported no survivors in his analysis of patients with LR and in a subsequent paper from the same institution, Bacci and colleagues [24–26] recommended that any patient with inadequate margins of excision of the primary tumour should be considered for immediate amputation in order to avoid the high risk of LR. In later publications, they have reported on 34 patients with LR of whom all but two were in association with metastases. In their series, three patients had metastases before LR, in 10 they were synchronous and in 19 the metastases were discovered later at a median of 4 months. Both patients who did not have metastases were treated by amputation and were cured but all of the other patients died. Their results are thus considerably worse than ours in terms of survival, although the proportions of patients developing metastases either before or after the LR is similar.

Taken in isolation, LR is undoubtedly an ominous development [27], but the significance of LR has not yet been investigated in a suitable multifactorial model and LR is not usually quoted as an independent bad prognostic factor for overall survival [28]. However, many of the factors which lead to LR are also those which lead to an increased risk of both metastases and death and thus LR may simply be a reflection of the combination of bad disease and inadequate surgical treatment. Most authors would agree that LR in isolation is not as bad a prognostic factor as the development of metastases [29].

We have shown that the development of LR is a particularly sinister finding in those patients with pre-existing or synchronous metastases. For them, no combination of treatment offers much hope of survival and even aggressive surgical removal of the LR and chemotherapy appear ineffective. This is not surprising as the vast majority will already have failed to show a response to initial chemotherapy and they may well have developed drug resistance in their recurrent disease.

However, for those patients without metastases, our results suggest a 41% chance of still being alive at five years after the LR. Whilst surgical excision is clearly mandatory, there is no clear evidence that chemotherapy is essential despite the 65% risk of these patients subsequently developing metastases. This situation is similar to the controversy relating to the routine use of chemotherapy in patients who develop metastases and which is as yet unresolved [30]. Unlike Rodrigues-Galindo and colleagues [10] we did not find that patients with late recurrence after one or two years was a good prognostic factor, but we agree that complete surgical resection of the LR is essential for cure.

Local control required amputation in 44 of 72 patients (61%) who had surgical excision, but was achieved by a local excision, and adjuvant radiotherapy in 39%. In general, the smaller LRs were adequately treated by excision and radiotherapy, whilst the larger ones needed amputation. Detecting LR earlier may well be beneficial both in terms of preventing the need for amputation and possibly decreasing the risk of subsequent metastases.

LR remains a signal of the failure of both systemic and local treatment in osteosarcoma. The prognosis for a patient with LR is marginally better than for

someone who develops a solitary metastasis. At the present time, surgery remains the mainstay of treatment, but given the high risk of subsequent metastatic disease developing there would be sense in including any patient with LR in a trial of chemotherapy for patients with metastatic disease who have undergone complete surgical resection. This should be part of a national or international protocol rather than a random decision, as was evident from our results.

Hopefully, more effective chemotherapy in the future will decrease the incidence of LR, but there will remain some patients in whom clear margins cannot be achieved with LSS and in these cases amputation will usually be the preferred treatment option, particularly if neoadjuvant chemotherapy does not appear to be effective.

Conflict of interest statement

None declared.

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